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ENCEPHALOMALACIA AND CAROTID ARTERY THROMBOSIS IN CHILDREN

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I. INTRODUCTION

A thrombus may be defined as a plug or clot in a blood vessel or in one of the cavities of the heart, formed by coagulation of the blood, and remaining at the point of its formation (2). Once it leaves its point of formation, it is known as an embolus. The thrombus or the embolus may cause an occlusion of a vessel, which leads to ischemia and infarction of the tissue supplied by the vessel. One of two types of infarction may occur: the "anemic-infarct" -- where the nectrotic tissue was supplied by end-arteries, and the "hemorrhagic infarct" -- where venous stasis has occurred allowing the area to remain filled with blood corpuscles. Necrosis is the end result of infarction, and two types of necrosis are recognized: Coagulation necrosis and Colliquation necrosis. The latter is a fluid-type of necrosis which is usually associated with brain tissue.

It has been stated that of all autopsies performed on adults, about 10 - 20% have shown forms of venous or arterial thrombosis. The former is more prevalent than arterial thrombosis. It is interesting to note that arterial thrombosis is found more frequently in women than in men and it occurs mostly between the ages of 30 - 80 years. It is seldom found under the age of 20 years.

The so-called "mixed thrombus" is the type which is most often dealt with in discussion of occlusive diseases. This is composed of fibrin masses with enmeshed erythrocytes, leukocytes and platelets. This type is differentiated from the "red thrombus" -- composed of adherent masses of red cells, and the "white thrombus" -- composed of conglutinated platelets and fibrin.

The factors which lead to occlusive thrombosis are:

1) an increase in blood viscosity
2) stasis
3) distortion of the vessel lumen due to certain "extrinsic" pressures
4) alteration in the integrity of the endothelium of the vessel.

Venous thrombosis is almost always occlusive in form, and it leads to local congestion, stasis, edema and ischemic necrosis. The fate of the arterial thrombus is most often embolization. It is interesting to note that most arterial emboli arise from mural intracardiac thrombi. Kimmonth, Rob and Simeone (7) list the reported sources of arterial emboli:

Condition	Percentage
Heart Diseases (all)	85-95 %
a) Auricular fibrillation rheumatic heart disease	(70-75 %)
b) Myocardial Infarction	(10-12 %)
c) Bacterial Endocarditis	(2-4 %)
d) Arterial Aneurysm	(1-2 %)
Atherosclerosis (mostly aortic)	2-3 %
Unknown and Miscellaneous	5-10 %

Table 1

The four common sites involved in arterial embolism are: the kidneys, the spleen, the brain, and the lower legs.

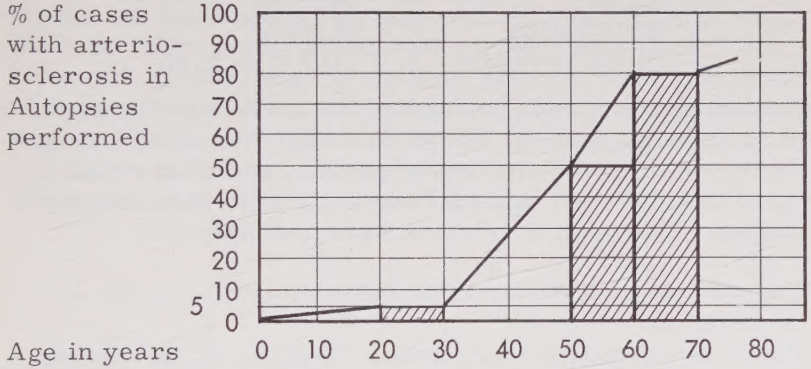
II. ETIOLOGY

The conditions which often lead to, arterial thrombosis and embolization are: arteriosclerosis, congenital heart

disease, sepsis, dissecting aneurysms and certain types of injuries (1).

Arteriosclerosis is characterized by the formation of atheromas, which are focal intimal lipid deposits. In time, these deposits become fibrotic and calcified. They tend to ulcerate into the lumen causing a thrombus formation.

Atheromas are rarely found un infants and young children. Autopsies reveal that the incidence of arteriosclerosis increases with increase in age. The following curve may demonstrate this:



(Curve is based on figures given by Robbins (14))

This condition usually results from long standing hypercholesteremia. In children, this may arise from Nephritis, juvenile diabetes, and other conditions. Mymin (11) reported sixteen cases of carotid artery occlusion due to arteriosclerosis in children under 10 years of age. Also, the following case of arteriosclerosis was reported by Duffy and Portnoy in 1957 (3) :

A 16 month old negro male was admitted to the hospital on July 3, 1956. One week prior to admission he had a "cold" with no productive cough, which lasted for two days. On July 1 he became irritable and anorexic. On July 2, he stumbled on his right foot and cried for a short time. The next day, his mother noticed that the sole of his right foot was pale and cooler than his left foot; the child also dragged his right leg. She also noted that the corner of his left lip was "drawn up" when he cried and that his head tilted to the left side. A physical examination revealed the following:

Temperature	=	98.6° F
Pulse	=	80/min.
Respiration	=	24/min.
Blood Pressure	=	110/ ? mm. Hg.

Both ear drums were perforated but there were no signs of acute inflammation. There was moderate anterior and posterior cervical adenopathy present and it was also noted that the right brachial and axillary arteries were dilated. The carotid arteries were not palpable.

The neurological examination obtained the following information:
The infant responded only to painful stimulation. He lay in bed with his left leg flexed at the knee and with his hip rotated externally. The right leg was also rotated externally. His right upper extremity was rigid and his right lower extremity was flaccid. Deep tendon reflexes were present bilaterally, but they were more active on the right side than on the left. The Babinski reflex was present on the right side and absent on the left side. The cremasteric and abdominal reflexes were active on the left side and absent on the right side.

The Kernig and Brudzinski signs were absent and his right eye was never completely closed.

Thirty-six hours after entering the hospital, the child died. A three hour post-mortem examination revealed an aneurysm and thrombus in the right axillary artery. The brain showed the cerebral hemispheres to be asymmetrical, the left side being larger than the right. There was flattening of the gyri and decreased depth of the sulci bilaterally but more marked on the left side. There was a thrombus in the left internal carotid artery which was grey-black in color, firm and adherent to the intima.

Within the putamen and globus pallidus, extending across the internal capsule, there was a cystic area about 1 cm. from side to side and the walls of the cyst were irregular and greyish. Microscopic diagnosis showed marked calcium deposits in the adventitia of the left internal carotid artery, and in the thrombus, the intima, the media and the adventitia of the Right brachial artery.

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Certain congenital malformations may cause thrombosis by increasing stasis in certain areas. Coarctation of the aorta is a prime example. The constriction usually occurs distal to the origin of the left subclavian artery. The diagnosis is based on finding a higher blood pressure in the upper extremities than in the lower extremities; normally the reverse is true. In a case presented by Mymin (11), this finding is classically demonstrated:

A 2 year old white female was admitted to the Royal Liverpool Children's Hospital for investigation, having recently recovered from an illness diagnosed as left ventricular failure associated with a respiratory infarct. She was to have a precordial systolic murmur. On admission there was no evidence of congestive failure and she was not dyspneic. The left radial and femoral pulses were diminished and delayed in comparison to the right. Her blood pressure measurements were as follows:

Right Brachial artery	=	180/130 mm Hg.
Left Brachial artery	=	135/85 mm Hg.
Right Femoral artery	=	110/90 mm Hg.

Both carotid pulses were palpable. Her toes were moderately cyanosed, but the fingers showed only slight cynosis. Her ECG showed biventricular hypertrophy. A Röntgenogram revealed a cardio-thoracic ratio of 0.69 and the pulmonary vascular markings were heavy.

Two weeks after her admission, she developed a left hemiparesis which improved in a few days. She became irritable after this incident and two weeks later, her carotid pulses could not be palpated. An angiograph showed direct filling of the descending aorta from the pulmonary artery via a patent ductus arteriosis. Three days later, the child's right hand and forearm became cold and blue. The right brachial pulse was palpable, but the radial and ulnar pulse disappeared. Heparin and Priscol were given and after a few days the limb improved. The color and temperature came back to normal. But the pulse recordings remained unchanged. One week after onset of this episode, the patient suddenly lost consciousness and died.

The post-mortem examination revealed an enlarged heart

with left ventricular hypertrophy. The pulmonary artery was larger than the ascending aorta. There was a patent ductus arteriosis and a constriction of the aortic arch between the left common carotid artery and the left subclavian artery. Adventitial hemorrhages were present over the root of the left common carotid artery, at the bifurcation of the innominate artery, and at the origin of the first branch of the right subclavian artery. Antemortem thrombi were found in the left common carotid artery, in the right common carotid artery, and the right subclavian artery (2 cm. distal to the origin, 1 cm. distal to the origin, and at the origin of the vertebral artery and extending 4 cm. distal, respectively). The brain showed small areas of softening in the right cerebral hemisphere, superior to the insula.
Histological examination of the aorta revealed many ulcerations and hemorrhages.

Heart malformations such as Tetralogy of Fallot, valvular conditions and patent ductus arteriosis are associated with thrombus formation. In 1945, Dr. R. E. Gross suggested that there may be extensions of thrombosis during the closure of either the umbilical artery or the ductus arteriosis, from which emboli may be released. This is a possible additional mechanism of arterial vascular accidents in small infants. He presented the case history of a thirteen month old male, who was found to have a right hemiplegia on admission to the hospital. The hemiplegia was of a twenty-four hour duration. The child's birth was normal, but after, he developed a cyanosis.

His heart was slightly enlarged and there was a prominent systolic murmur on auscultation. Clubbing of the fingers and toes was present. Tetralogy of Fallot was suspected.

Three weeks before hospitalization, he vomited and showed progressive muscular weakness with a tendency to fall to the right side. One day before admission, the child went into a deep stupor and twelve hours later, he developed a complete paralysis of the right arm and leg. The neck was stiff, the Babinski was present on the left side and questionably on the right side. The blood picture showed the white count to range from 6,200 to 15,000 (seven counts were taken), and the red count was never below 7 million/cmm. The spinal fluid was clear and showed a normal pressure with a total protein of 13,3 mg, no red blood cells present and 5 white blood cells present (polymorphs).

On the eighteenth day after admission, a small ecchymotic area of 2 cm diameter appeared on the surface of the left heel. Within the next twenty-four hours, it spread throughout the whole lower leg. The femoral artery revealed no pulsation on the left side, although it was good on the right side. The left lower leg became progressively bluer and cooler. The child died on the twenty-third day of admission. The post-mortem examination revealed the presence of a Tetralogy of Fallot, a thrombus in a patent ductus arteriosis, and an occlusive thrombus at the base of the brain of the left internal carotid artery. There was extensive cerebral degeneration and softening predominantly on the left side of the brain. There were thrombi present in the superior longitudinal sinus and within the cerebral veins. Also present was a thrombus in the abdominal aorta, just above the renal arteries.

Bacterial or hyperallergic conditions of the heart valves, such as subacute bacterial endocarditis or rheumatic fever, often lead to thrombosis and embolization. The warty valvular lesions of bacterial endocarditis are composed of bacteria and blood cells. Other organisms such as the meningococcus and the rickettsias have a special affinity for the endothelial lining of blood vessels. They ulcerate into the walls and cause hemorrhage and thrombosis.

In 1961, H.S. Wisoff (22) discussed the role of dissecting aneurysms as an etiology of cerebral arterial thrombosis. He reported a case of an eleven year old, negro female with a left hemiparesis, who was admitted to the Bronx Municipal Hospital Center on September 21, 1957. The child had been in good health and had a negative medical history except for an episode of minor head trauma one year previously.

During the previous two weeks she had intermittent, mild right sided headaches, but this did not interfere with school work or usual play. On the day of admission, while at play, she suddenly developed a more severe right sided headache and collapsed because of weakness of the left leg. The child was brought directly to the hospital. Her temperature was 98^{o} F, pulse 88, respiration 16, and blood pressure 120/60 mm Hg. The child was well developed and moderately obese. The general physical examination revealed no abnormalities. She was drowsy, but well oriented and able to present the details of her illness. There was slight tenderness over the right temple.

The pupils were normal with the eyes in forced conjugate deviation to the right. There was a clear cut dense, left homonomous hemianopsia. The optic fundi were normal. There was marked hemiparesis including the face, with a left Babinski reflex present, depressed abdominal reflexes on the left side, and hyporeflexia of the left arm and leg. A left sided hemisensory defect was also present to all stimuli. The carotid pulsations in the neck were normal, and no bruit was audible in the neck or skull. The lumbar puncture showed 12 red blood cells and 1 white blood cell, the protein was 11 mg% and the sugar was 98 mg%. An EEG revealed considerable disorganization on the right side of the brain, with medium to high amplitude, poorly formed waves and a small amount of activity. On the left there was moderate disorganization with medium, irregular waves.

The child improved during the first forty-eight hours of hospitalization. On the third day, however, she was considerably more uptonded with a complete left hemiplegia and a beginning right third nerve palsy. Bilateral percutaneous, carotid angiography was performed under general anesthesia.

This revealed complete obstruction of the right internal carotid artery above the siphon. The left sided injection revealed normal internal carotid, middle cerebral and posterior cerebral arteries. The left anterior cerebral artery was bowed from right to left, the right anterior and middle cerebral arteries were very faintly visualized. The child was allowed to awaken from anesthesia and again appeared to improve. On the following day however, she was deeply stuperous. An exploratory right frontal craniotomy was undertaken in hopes of finding an intracerebral hematoma and / or

an associated deep frontal vascular malformation. At operation, the brain was under considerable increased pressure. Transcortical exploration was carried down to the region of the head of the caudate nucleus without encountering any abnormalities except for edematous, ischemic brain tissue. The child remained in deep coma post-operatively and died forty-eight hours later.

The post-mortem examination took place six hours after death. There was a diffused, moderately severe bronchial pneumonia with a small sub-pleural hemorrhage over the right lower lobe. The heart was normal, except for the coronary arteries which showed focal intimal thickening. The brain showed considerable softening of the right frontal, temporal and parietal lobes. A brown thrombus was present within the stump of the right internal carotid artery, which extended into the proximal portions of the anterior, and middle cerebral arteries. The right common, internal and external carotid arteries in the neck were free of thrombi. Gross examination of the aorta and systemic vessels revealed no abnormalities. Microscopic examination of the right internal carotid, the proximal anterior and middle cerebral arteries revealed the internal elastic membrane to be fragmented, with a large thrombus present between the intima and media reducing the lumen to a narrow, convoluted slit at one side. The right middle cerebral, left subclavian, innominate, superior mesenteric, and renal arteries all revealed focal areas of medial necrosis. Elastic tissue stains also showed loss and fragmentation of the elastica in the areas adjacent to the medial degeneration.

Aneurysms of the large blood vessels are supposedly rare in early life. Many such cases are attributed to syphilis. Dissecting aneurysms of the aorta are usually associated with Marfan's syndrome. This syndrome involves malformations of the skeletal system along with such congenital defects as subluxation of the optic lens and a malformed aorta with thinning and weakness of the media.

Another cause of carotid artery occlusion was presented and discussed by Brando (1) in the March 1956 issue of the British Medical Journal. He wrote of several cases concerning injuries sustained by children who fall on pointed objects with their mouths opened. He associated these injuries with carotid artery occlusions found on autopsy.

In 1959 Stevens (19) presented two cases of carotid arterial occlusion in children. One of these cases recovered with the help of anticoagulant therapy.
A word of caution was discussed by Shimaoto (17) on anticoagulant therapy in patients with arteriosclerosis. The anticoagulant may induce bleeding within an atheromatous plaque, which in turn would cause the occlusion. Also, some authors caution against using certain dyes, such as iodopyracet, in angiography, because these induce vascular injury.

To summarize this review of case histories in the literature, the following can be stated:
Of the thirteen cases reviewed, four children had cardio-vascular anomalies, two children had dissecting aneurysms, three children sustained injuries which may have caused carotid thrombosis, three cases could not be attributed to any specific etiology, however one of these could have been due to an infectious process and one case can be attributed to arteriosclerosis.

However, it is also important to note that Mymin reported sixteen cases of carotid arterial occlusion due to arteriosclerosis in children under ten years of age.

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Author	Patient	Suspected etiology & Associated Disease
Gross	2 wk. ♀	Dilatation of duct. arteriosis with thrombosis, emboli to pulm. circ.
Gross	13 mo. ♂	Tetralogy of Fallot & thrombosis in pat. duct. arteriosis.
Teng	5 yr. ♂	(fever, sore throat, abdom. cramps) sepsis? UNKNOWN
Stevens	5 1/2 yr. ♀	UNKNOWN
Stevens	1 yr. ♀	Endocardial Fibroelastosis with thrombi in 2 branches of medial cerebral arteries. Angiograph showed occlusion of right carotid -- but not seen on Autopsy.

(continued on next page)

Duffy	16 mo. ♂ (negro)	Arteriosclerosis + Dissecting aneurysm in axillary artery.
Goldstein-Burgess	7 yr. ♂	UNKNOWN
Mymin	2 1/4 yr. ♀	Constricted Aortic arch, hypertrophy of left ventricle, pat. duct. arteriosis.
Wisoff	11 yr. ♀	Dissecting Aneurysm
Wisoff	3 yr. ♂ (negro)	
Brando	3 cases	Injury with pointed object into palate of mouth thrombosis of carotid artery.

Table 2

Summation of cases reviewed in the literature

Cardio-vascular anomalies	= 4	
Unknown	= 3	
Arteriosclerosis	= 1	(+ 16 cases reported by Mymin)
Dissecting Aneurysms	= 2	
Brando's Injury to mouth	= 3	
Total number of cases	= 13	

III. CAROTID ARTERY OCCLUSION AND THE BRAIN

When the blood supply to the brain is interfered with, anoxia of the brain tissue results. Immediately after the occlusion of the vessel, the affected part of the brain may be pinkish and swollen due to the associated collateral hyperemia and edema. After two to three days, the area becomes very soft and there is a loss of demarcation between the grey and white matter. Liquifaction and cyst formation usually result, and this is referred to as the Colliquation necrosis.

The clinical symptoms may include drowsiness, apathy, unconsciousness, convulsions, head retraction with flexion of the arms and extension of the legs, and hemiplegia.

Occlusion of the internal carotid artery effects the anterior and middle brain areas. The immediate manifestations are vertigo, headache, hemiplegia and loss of consciousness. Autopsy reveals cerebral softening and microgyria (small, malformed brain convolutions).

IV. CASE PRESENTATION:

This is the case presentation of an eight hour old male infant. His mother had a touch of the "Grippe" between the second and third month of pregnancy, which could have been Rubella. The child was third in the family and the other two children were normal. On May 18, 1960, the mother accidently fell; two days after, she felt the labor pains and on May 26 she gave birth. The birth process took four and one half hours and the birth was spontaneous in a normal presentation.

He was however in a blue cyanotic state at birth. His birth weight was 1070 grams with a length of 36.5 cm. Other findings were a hemangioma on the left cheek, and a bilateral congenital cataract. The reflexes and musculature were considered within normal limits.

The child's respiration progressively became irregular and he took on a grey complexion. The child was put on Micoren and Penicillin. Micoren is a drug which enlarges the respiratory amplitude with little change in respiratory frequency (Geigy). This treatment, however, did not improve the child's condition; instead it became worse. At 3 : 20 am, the child stopped breathing and his heart-beat stopped shortly thereafter. Vomitus of brown-black color had to be sucked out many times. The stomach had a large quantity of this material, but no bacterial pathogens were found.

The post-mortem examination revealed the following information: The liver showed the parenchyma to be hyperemic, the renal epithelium showed some opaque swelling, the lungs showed signs of aspiration and large atelectatic areas were found -- these areas appeared as if they had not as yet been in use; no hyaline membrane was found. The myocardial tissue and the spleen showed hyperemia (the spleen showed no malpigian corpuscles). The spinal cord showed areas of passive hyperemia with areas of softening. There was a thrombus in the right common carotid artery, and swelling of the intima was present. The thrombus was judged to be a relatively "old" one as opposed to a fresh one. No inflammatory signs could be recognized. The brain showed liquifaction in the cerebrum and cerebellum.

In summation, the autopsy diagnosis reads as follows:

1) Thrombosis of the right common carotid artery.
2) Aspiration Pneumonia and atelectasis.
3) Uric acid infarct of the right kidney.
4) Liquifaction of the brain.

V. DISCUSSION OF THE POSSIBILITIES OF THIS CASE:

The author has already discussed the etiologies of thrombus formation from the literature. However, one particular possible etiology has not been discussed and it is one which has received a lot of attention in the literature in the past few years, that of Intrauterine Rubella or "maternal rubella". The possibility exists that the case just presented, could very well have been attributed to maternal rubella.
The common anomalies found in these children are: microcephaly, deafness, cardiac anomalies, and congenital cataract.

Lock, Gatling and Wells (9) examined 176 children for evidence of congenital anomalies via maternal rubella exposure. The first examination took place at 4 - 12 months, and the second examination took place at 16 - 25 months. In the first examination, the authers had found that 35 infants had 32 definite individual anomalies and 27 were doubtful anomalies. On the second examination 7 of the 27 were found to be significant:
2 heart disease, 3 mental deficiency, and 2 deafness . . . also 12 previously unsuspected anomalies were discovered, of which 11 were serious. There were cases of microcephaly, deafness, mental deficieny and retinal degeneration.
Steen and Torp (18) reported cases of Encephalitis and Thrombocytopenic purpura which were attributed to maternal rubella.

The most recent study was reported by Rudolph, Yow, Phillips, and Melnick in JAMA of March, 1965 (15). Twenty-five infants whose mothers had had rubella during pregnancy were studied. The majority showed growth retardation, hepatospleenomegaly, purpura and congenital cardiac and eye defects, also microcephaly and Glaucoma.

Thrombocytopenia was a constant finding and there was also an increased cerebro-spinal-fluid pressure and some pleocytosis. The purpuric lesions varied from discrete dark blue lesions which were generalized over the body to particular distribution over the face. Some bone lesions were described as a trabecular pattern, consisting of small longitudinal areas of radiolucency in the metaphysis of long bones. Also reported was the isolation of the virus mostly from throat and rectal swabs. It was also isolated from the urine of three children.

Lorant and Radl discussed embryopathies following German measles during pregnancy in the epidemic of 1961 in Austria. They studied 89 cases, 33 were early pregnancies and 24 were full term pregnancies. Among them were three typical cases of virus embryopathy: cataract and heart anomalies. However, there is no report of death via carotid thrombosis due to maternal rubella.

Other factors must be included into our discussion: first, many of the children born under the influence of maternal rubella are born prematurely, and a premature child is more vulnerable to disease and is relatively weaker than is a full term child.

The causes for premature birth are:

1) factors which increase irritability of the uterus and cause it to reject an otherwise normal fetus.
2) abnormalities in the placenta which disturb circulation or promote early separation.
3) lesions in the fetus which lead to expulsion by an otherwise normal reproductive apparatus.
4) common causes from mother's side:

    a. Tuberculosis
    b. Syphilis
    c. Trauma
    d. Surgical procedures

It is also important to note in this discussion, that large areas of the lung in a premature infant may be incapable of expansion because alveolar sacs have not yet developed.

The major causes of neonatal mortality for premature infants in the 1001 - 2500 gram weight area are: hyalin membrane disease, malformations, intra-uterine anoxia, trauma, pneumonia and erythroblastosis (6).

One can only speculate as to the cause of thrombus formation. Intra-uterine rubella and trauma are high on the "suspect list", but this is by no means conclusive. There were no heart anomalies present to suspect this as a cause and none of the other etiologies discussed in the literature come into play in this particular case.

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SUMMARY:

The basic pathology and suspected etiologies of carotid thrombosis have been presented. Thirteen cases of carotid thrombosis from the literature have been reviewed and four of these have been presented in full, in order to represent the leading conditions which are associated with the condition being discussed.

The case of an eight hour old male child, admitted into the Basel Children's Hospital has been presented, along with a discussion of intra-uterine rubella and trauma as possible causes for carotid thrombosis.

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Curriculum vitea

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